REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The specification has been revised to delete the amendments to the specification introduced by the Amendment dated May 22, 2007.

The claims have been revised to define the invention with additional clarity. The claims as presented are fully supported by an enabling disclosure. For the sake of completeness, the basis for the amendments made to claim 32 is highlighted in the Table below:

Amendment to claim 32	**Basis**
reference to a promoter	claim 37 and paragraph [0018] of the description
reference to a signal sequence	claims 55 and 56 and paragraphs [0036], [0037] of the description
reference to a heterologous antigen	claim 33 and also in the description at paragraph [0083], [0088] and [0094]
reference to a chimeric gene	claim 34
reference to oral administration	paragraph [0022] and [0030] of the description

Claim 75 has been amended to include the same features as amended claim 32.

Claims 33-35, 45, 46, 48, 51, 60-66, 70-73 and 76-79 have been cancelled without prejudice.

Elections/Restrictions (Items 1 to 5 of the Official Action)

Applicant gratefully acknowledges the Examiner's indication that, once product claims are considered allowable, process claims of an equivalent scope may be rejoined. The same amendments made to claim 32 have also been made to claim 75 to preserve the right to rejoin the product claims.

Claims rejections – 35 USC § 101 (Item 9 of the Official Action)

In order to facilitate prosecution, claim 32 has been amended to refer to a "*heterologous antigen*" being encoded by the genetic construct of the *Bacillus*. Accordingly, what is claimed is distinct from anything occurring naturally and the invention does show the hand of man.

Reconsideration is requested.

The specification (Items 10 to 13 of the specification)

As indicated above, the specification has been revised to delete the amendments introduced by the Amendment dated May 22, 2007. That the specification has been revised should not be construed as an indication that Applicant agrees with the Examiner's position as regards new matter. In this regard, it is noted that the Examiner specifically comments on *rrnO* and argues that *rrnO* was not indicated to encode a ribosomal RNA. However, the skilled person would be aware that rrn genes encode ribosomal rRNAs. For instance, a Medline abstract is for Itaya *et al* (1993) *Biosci Biotechnol Biochem* 57(9): 1611 –1614 is submitted herewith which refers to rrn genes as encoding ribosomal RNAs. The Examiner is requested to initial and return the attached Form PTO/SB/08a listing same.

Reconsideration is requested.

Claims objections

Referring to the numbered points of the Office Action:

15. Claim 32 has been amended to replace the colon and semi-colons objected to with commas. The claim is now a single sentence using only commas as requested.

16. Claims 34 and 35 have been deleted rendering moot the objection raised in respect of those claims. Claims 37 and 39 have been amended to replace reference to a "*gene construct*" with reference to a "*genetic construct*". The wording of claims 37 and 39 is therefore consistent with that of claim 32.

17. It is possible to adapt an antigen to enhance its ability to elicit an immune response as specified by claim 43. For instance, fusing an antigen to another protein may make it more immunogenic and hence better modified to elicit an immune response against the antigen. Reference to an antigen being adapted to elicit an immune response would be well understood by the skilled person and it is respectfully submitted that claim 43 is clear (likewise, claim 44).

18. Claim 44 has been amended so that it refers to Tetanus Toxin C which was the elected invention.

19. Claims 60 and 61 have been deleted rendering the objections raised against those claims moot.

20. Claim 33 has been deleted rendering the objection raised moot.

Reconsideration is requested.

Claims rejections 35 USC § 112, second paragraph (Items 21 to 27 of the Official Action)

Referring to the numbered points of the Officel Action:

22. Claim 32 has been amended to delete the reference to "*said protein*".

23. Claim 36 has been amended to delete the reference to a *"vector"* and *"genetic modification"*.

24. In order to facilitate prosecution claims 47, 49 and 50 have been amended to make clear that the protein being referred to is the vegetative cell protein of claim 32, part (ii). Claims 45, 46, 48 and 51 have been cancelled, thereby rendering moot the rejection thereof.

25. The preferred embodiments previously present in claim 59 have been made the subject of new dependent claims 80 and 81, thereby addressing the second aspect of the rejection presented in Item 25.

In respect of the first aspect of the rejection, claim 59 (and new claims 80 and 81) do not omit essential features. All of the necessary structural connections are specified by the claims. In particular, the ability to bring about active secretion and Type I, II or III secretion is a function of the signal sequence selected. The cell will inherently possess the ability for all of Types I, II and III secretion, it is the signal chosen which defines which of Types I, II and III occurs. The same reasoning applies for glycosylation. There are, therefore, no essential features missing from the claims in question because the *Bacillus* inherently possesses the ability of Types I to III secretion and also glycosylation.

26. This rejection has been rendered moot by the cancellation of claims 60 and 61.

27. Claims 65, 66 and 71-73 have been cancelled thereby rendering moot the rejection thereof.

Reconsideration is requested.

Claims rejections 35 USC § 102 (Items 28 and 29 of the Official Action)

In respect of the Examiner's comments on the previous amendments to claim 32 regarding the fact that the claim has been amended to refer to a signal sequence, vegetative cell protein and the *rrnO* gene, it is respectfully submitted that all three alternatives should be considered.

In particular, as a signal sequence is a form of targeting sequence and the claim originally referred to the use of a vegetative cell protein, both were originally referred to in the claims, as was *rrnO* in dependent claim 49. Given that the amended claims are directed to subject matter covered by the original claims, it is respectfully submitted that all three alternatives should be considered.

As regards the lack of novelty rejection, the subject matter of the claims is not anticipated by US 2002/0150594 for the reasons set-out below.

US 2002/0150594 does not disclose the specific combination of elements specified by claim 32. In order to facilitate prosecution, claim 32 has been amended to refer to a *Bacillus* spore where the *Bacillus* encodes a "*heterologous antigen*":

(i) linked to a signal sequence,

(ii) as part of a chimeric gene with a vegetative cell protein, or

(iii) as part of a chimeric gene with the *rrnO* gene.

All of possibilities (i) to (iii) mean that the heterologous antigen will only be expressed after germination of the spore, during vegetative cell growth. Such a combination is not disclosed in US 2002/0150594.

In particular, there is no disclosure in US 2002/0150594 of a heterologous antigen being linked to such sequences as (i) to (iii) thereby meaning that heterologous antigen expression is

linked to germination and vegetative cell growth. In US 2002/0150594, the antigens are expressed as fusions with spore coat proteins.

The Examiner makes reference to the fact that US 2002/0150594 refers to a heterologous antigen in Tetanus Toxin Fragment C. However, the TTFC is not linked to any of the possibilities (i) to (iii) specified by claim 32. In particular, page 23, paragraph [0190] of US 2002/0150594 refers to TTFC amongst a long list of antigens and then states at the final part of the paragraph:

"having antigens expressed or displayed on the spore surface" [emphasis added]

It is therefore apparent that what is disclosed is expression at the spore surface and in particular as a fusion with a spore coat protein. There is no disclosure of linking expression to vegetative cell growth via any of the elements (i) to (iii) specified by claim 32.

The Examiner also makes reference to a number of other passages of US 2002/0150594. In particular, paragraph [0180] at page 22 is cited as disclosing a ribosomal rRNA gene. However, paragraph [0180] of US 2002/0150594 is concerned with:

> "Temperature sensitive (Ts) mutations: A temperature sensitive mutation in a gene that is essential for bacterial growth and replication (such as a gene that encodes one or more subunits of a DNA polymerase or ribosomal RNA/protein)"

Reference to the use of mutations in the natural occurring ribosomal RNA of a *Bacillus* for selection purposes is not the same as forming a chimeric gene where sequences encoding the heterologous antigen are linked to rRNA sequences as specified by claim 32. There is a difference between an endogenous gene being mutated and such a chimeric gene as that specified by claim 32. The subject matter of claim 32 is clearly not anticipated by US 2002/0150594.

Similarly, the Examiner cites Widom *et al* (1988) as showing that *Bacilli* have endogenous ribosomal RNA genes, but the same argument applies. Namely, the fact that a

Bacillus has endogenous ribosomal RNA genes is not the same as using an artificially generated chimeric gene with a fusion of coding sequences for a heterologous antigen and sequence from the *rrnO* gene.

The Examiner also cites page 10, paragraph [0097] of US 2002/0150594 as referring to the use of a signal sequence, as well as citing paragraphs [0094] and [0098] in that regard. However, none of these passages refers to linking expression of a heterologous antigen to a signal sequence so that the antigen will only be expressed following germination and vegetative cell growth. Those passages do not refer to expression of heterologous antigens. Where the application discusses antigens, it is apparent that it does so in the context of the heterologous antigen fused to a spore coat protein and hence the antigen being expressed is not linked to spore germination and vegetative cell growth as it is in the spore referred to in claim 32.

Indeed, it is important to note that US 2002/0150594 is not just concerned with the expression of antigens. As outlined in paragraph [0038] of US 2002/0150594, the *Bacilli* referred to can be used for an array of purposes, including in industry. Industrial use is expanded on in paragraphs [0065] to [0072] of US 2002/0150594. US 2002/0150594 also discusses the use of the *Bacilli* in display systems and as diagnostic tools in detail over paragraphs [0073] to [0075] and in a wide range of other applications at paragraphs [0076] to [0091].

Thus, the general passages referred to by the Examiner should not be construed as indicating use of a signal sequence to expression heterologous antigens to produce spores that will be suitable for oral vaccination, as specified by the claims of the present application. US 2002/0150594 does not disclose that, it only discloses heterologous antigens as fusions with spore coat proteins. Thus all that is disclosed in US 2002/0150594 is a heterologous fusion of

protein with a spore coat protein and not a heterologous antigen the expression of which is dependent on vegetative cell growth as claimed in the present application.

The fact that US 2002/0150594 only discloses expression on the spore surface is also evident from paragraph [0042] of US 2002/0150594 which states that:

> "*Any antigen of interest or antigenic fragments thereof, **can be displayed on** the spore to produce an immune response*" [emphasis added]

The use of the word "*on*" again indicating that the antigen is to be expressed on the spore surface.

That is well illustrated by the Examples of US 2002/0150594 which do deal with expression of heterologous antigens. For instance, in Example 1 of US 2002/0150594 at page 36, paragraph [0278], halfway down, US 2002/0150594 states that:

> "*The expression vectors further comprise linker sequences in order to easily ligate an assortment of clones into the vectors so as to be operably linked with the **cotC full-length nucleotide sequence** or fragment thereof*" [emphasis added]

Thus, what US 2002/0150594 discloses is fusing heterologous antigens to spore coat proteins such as cotC.

That is also apparent from Example 2, page 37, paragraph [0279] which refers to fusion to CotC as does Example 3 at page 38, left hand column, paragraph [0288]. Indeed, all of the Examples dealing with expression of a heterologous antigen in US 2002/0150594 refer to the antigen being fused to a spore coat protein. There is, therefore, no disclosure to express a heterologous antigen in any of the ways specified by claim 32.

Thus, in US 2002/0150594, where a heterologous antigen is expressed, it is expressed on the cell surface of the spore as a fusion with a spore coat protein. US 2002/0150594, therefore,

uses the spores themselves, and the spore coat proteins present thereon when producing *Bacilli* for vaccination.

It will be apparent from the foregoing that US 2002/0150594 does not disclose the subject matter of the instant claims and, thus, the rejection of the claims as anticipated (inherently or otherwise) is not well founded. Reconsideration is requested.

The instant invention would also not have been obvious over US 2002/0150594.

At the time of the invention, it would not have been obvious to link expression of a heterologous antigen to spore germination. Documents such as US 2002/0150594 were firmly focussed on fusing antigens to spore coat proteins so germination was not required and hence directing the skilled person away from the invention.

If using spores to express a heterologous antigen for vaccination, the skilled person would want to ensure that the subject being vaccinated would be exposed to the antigen.

At the time of the invention the skilled person would have considered that spores would not be able to germinate when orally ingested at a level that would mean that an antigen, the expression of which was dependent on germination, would be expressed at adequate levels to successfully elicit an immune response. The demonstration in the Examples of the present application that it was possible to elicit an immune response where heterologous antigen expression was dependent on vegetative spore growth was, therefore, surprising.

The gastrointestinal tract, and particularly the stomach, represent harsh environments damaging to spores and any germinating spores in particular. The successful germination of the spores of the invention at a high enough level to elicit and immune response was, therefore, unexpected.

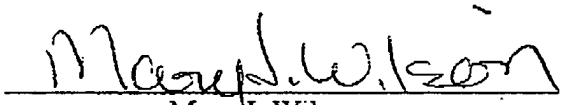
The attention of the Examiner is drawn in the present application to Example 1, at page 20, section (e) and Example 2, pages 30 and 31 and to Example 2 and Figures 8A and 8B of the present application which demonstrate that unexpectedly high levels of spores germinate into vegetative cells in the GIT giving rise to enough antigen expression to successfully elicit an immune response proving the efficacy of the invention.

Given the focus in US 2002/0150594 on fusing a heterologous antigen to a spore coat protein, particularly illustrated by the Examples of US 2002/0150594, the skilled person would not have linked expression to germination and arrived at the invention. The skilled person simply would not have considered it would work because the artisan would not have considered that germination would occur and the antigen would be expressed at a high enough level to elicit an immune response. The skilled person would not have produced the spores of claim 32. The subject matter of the claims would, therefore, not have been non-obvious.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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